REMARKS

Claims 1 and 4-23 have been presented for examination and stand rejected.

Claims 1 and 4 have been amended to further describe the hetero forms of certain groups comprising R^2, R^3 or R^4. Support for this description is provided throughout the specification, for example in paragraphs [0018]-[0021].

Claims 20 and 23 have been canceled. New claims 24-27 have been added: claim 24 is supported by, for example, paragraph [0026]. Claims 25-26 are supported by canceled claim 23, and relate to use of the compounds and compositions of the invention for treatment of liver fibrosis. No new matter is added by the amendments. Entry of the amendment is respectfully requested.

Rejections based on 35 USC 112

Claims 1 and 4-23 were rejected as allegedly indefinite because certain groups were described in part by the term "hetero forms thereof". The applicant disagrees with the allegation that this term is indefinite, as it would be understood by those skilled in the art, especially when read in view of the specification. Nevertheless, solely to place the claims in condition for allowance, claims 1 and 4 have been amended to further describe the "hetero forms" of the named groups. In view of the amendment, this rejection can be withdrawn.

Claim 20 was rejected as allegedly not enabled. Solely to place the claims in condition for early allowance, that claim has been canceled. This rejection is therefore moot.

Rejections under 35 USC 103

Claims 1 and 4-23 were rejected as allegedly obvious in view of Cai, et al., WO 02/47690. This rejection is substantially identical to the one previously presented, and is described by the examiner as being "maintained".

The applicant traverses this rejection for the reasons previously presented, and reinforces those arguments with the following remarks based on a very recent Federal Circuit case precisely on point, Takeda v. Alphapharm, 06-1329 (June 28, 2007). *Takeda* relates to obviousness in a chemical invention. It arose in the context of a litigation matter, but the court did not rely on a presumption of validity for its analysis at all: it held that no *prima facie* case for an obviousness rejection was provided, because there was not sufficient evidence that one of ordinary skill would have been motivated to select a particular species from the reference as a starting point, or to make the "specific molecular modifications" needed to arrive at the claimed invention.

Takeda is highly relevant and clarifies the burden for establishing obviousness of a chemical invention that remains applicable even after *KSR v Teleflex*. The *Takeda* opinion says that while a known compound may suggest its homolog, analog or isomer,

> in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required.

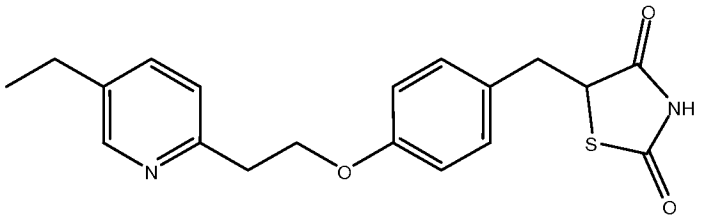
Takeda slip op. at 9 (emphasis added).

To underscore that this is **not** a litigation rule, note that the court quoted from In re Deuel (51 F.3d 1552, 1558 (Fed. Cir. 1985), and cited In re Jones, 958 F.2d 347 (Fed. Cir. 1992); In re Dillon, 919 F.2d 688; In re Grabiak, 769 F.2d 729 (Fed. Cir. 1985), and In re Lalu, 747 F.2d 703 (Fed. Cir. 1984) as supporting, consistent authority for that statement. The court thus indicated that it was applying the same standard that must be met outside the litigation context for establishing *prima facie* obviousness of a chemical invention.

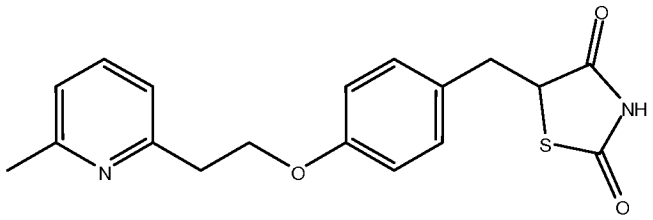
For the Examiner's reference, the compound Takeda claimed (Actos) and the prior art compound that Alphapharm relied upon for its obviousness theory (Compound b) are depicted below. The prior art described a genus and 53 specific compounds (including compound b) within the genus, and Takeda conceded that the genus encompassed Actos. Despite the similarity between Actos and the prior art compound, and even though the prior art genus admittedly encompassed

Actos, the court held that *prima facie* obviousness was ***not*** established for either Actos *or* a genus including the other Ethyl-substituted pyridine analogs of Actos.

ACTOS™



Compound b



In *Takeda*, the cited reference related to the same biological activity as the activity of the compounds in the claimed invention. It was admitted by the patentee that the prior art genus encompassed the later claimed invention. In *Takeda*, the claims, which were not rendered obvious by the very similar prior art genus and species, included both species *and* subgenus claims. The prior art included a *species* ('compound b', the 6-methyl derivative) that was a homolog of compounds within the scope of the subgenus claims. The subgenus and species claimed by Takeda each required an Ethyl group: the Ethyl could be at any of positions 3-6 in the subgenus, and was specifically at position 5 in Actos. Nevertheless, the claim to the 5-ethyl compound Actos *and* the sub-genus claims, which permitted ethyl to be at positions 3, 4, 5, or 6, were held to be **nonobvious** over the 6-methyl compound (compound b), because there was no evidence leading one of ordinary skill to produce the compounds in the scope of the claim based on the teachings of the prior art. Also note that the court in *Takeda* expressly stated that no *prima facie* case of obviousness had been established; therefore, there was no need to consider the secondary evidence of non-obviousness. Thus, while such evidence was discussed, the holding rested on the fact that no *prima facie* case for an obviousness rejection was established, so no rebuttal evidence was needed by the patentee.

The present rejection ultimately relies only upon the fact that certain compounds within the scope of the claims would also allegedly be within the scope of the prior art claims. If that were sufficient to create an obviousness rejection, the result in *Takeda* would have been different: the claimed species and subgenus in *Takeda* were both admittedly within the scope of the prior art genus. Thus *prima facie* obviousness is not established by showing that the prior art genus permits selection of molecular features to produce a compound in the claim scope, the prior art must provide a reason to make a particular compound within the scope of the claims. That has not been shown in this case.

The present rejection is based in part upon certain species that the Examiner selected from the cited reference. However, as was the case in *Takeda*, the reference did not provide reason to select those species. The cited reference in this case lists *hundreds* of compounds in a list of compound names that occupies more than 20 pages, and the Examiner has given no reason to select the ones that the rejection is based on: those were selected entirely based on the applicant's disclosure. The present disclosure is not part of the prior art; thus a person of ordinary skill would not have known to SELECT the particular species that the rejection relies upon as a starting point. Like the situation in *Takeda*, where the court concluded that the 6-methyl species was selected without any guidance from the prior art and was thus not properly identified as a starting point for an obviousness analysis, the Examiner has not shown proper motivation to start with any of the species in Cai that were identified as starting points for the obviousness analysis.

Moreover, even if a starting point were properly selected, it also must be MODIFIED to arrive at the claimed invention. *Takeda* makes it Very clear that the prior art must provide motivation to make the ***"specific molecular modifications"*** necessary to arrive at the claimed invention. That, too, has not been shown in this case. Nothing in the reference explains why one would have made the particular modifications of any species from Cai that the rejection relies upon: the rejection distils down to an assertion that such modifications would have been obvious because the claimed genus allegedly overlaps with the prior art, thus those modifications are permitted by the prior art genus. According to the Examiner, "Again, as pointed out reference clearly permits phenyl in position of the pyrimidine ring. Hence, contrary to applicants' urging, it would be

obvious to one trained in the art that 2-phenyl substituted pyrimidines bearing pyridylamino, indoylamino, pyrimidinylamino and benzimazoyl [sic] amino groups at the 4-position would also have the same use taught in the reference." Again, though, this standard on which the Examiner relies contradicts the standard in *Takeda* and prior Federal Circuit case law that is cited in *Takeda*. The fact that the prior art genus "permits" such modification is simply insufficient as demonstrated by *Takeda*. A prior art genus **does not, as a matter of law, render obvious all it encompasses:** the dissent in *Takeda* would have applied such a rule, but the majority in *Takeda*, and the case law they relied upon, *i.e.*, the prevailing law on obviousness says that falling within a prior art genus is not sufficient to establish obviousness.

The reality is that the cited reference discloses a very broad genus, and many, many species, any one of which could be modified in dozens if not thousands of ways. With no further guidance from the reference, the person of ordinary skill would have had no way to select a starting point and know how to modify it to arrive at the invention now claimed. The Examiner argues that the claimed invention is obvious by looking at the Applicants' disclosure, to pick and choose compounds in the prior art as starting points for modification. Then the Examiner *again* looks at Applicants' disclosure to select the ways to modify the chosen species. No other way has been shown to get to the claimed invention. *Takeda* clearly indicates that guidance from the prior art is required for the selection and modification of the prior art species, **even in a situation where few changes are needed**.

Again, look at the similarity between Compound b and Actos: Actos was NOT rendered *prima facie* obvious by Compound b disclosed as part of a genus that encompasses Actos. In that case, the claimed invention included a homolog or an 'isomer of a homolog' of a species in the prior art. Nevertheless, the *Takeda* court held that the prior art did not provide one of ordinary skill guidance to select that starting point or motivation to make the "specific molecular modifications" to arrive at the claimed invention; as a result, no *prima facie* case of obviousness was established. Likewise here, the only motivation to select the starting points relied upon by the Examiner is the present disclosure, which is clearly not part of the prior art. The current rejection states that the reference "permits" the particular modifications, and points to a few isolated species among the

hundreds listed that include a 2-phenyl group, but the phenyl group is only in combinations that are clearly not within the scope of the claims. Again, the only reason to make the particular modifications needed to arrive at the present inventions is also the applicants' disclosure, which again is not part of the prior art. Such hindsight-based analysis is plainly insufficient to establish a *prima facie* case of obviousness for a chemical invention, as is amply illustrated by *Takeda*.

The Examiner stated that "alternate substituents taught in the reference for the pyrimidine core would result in compounds with the use taught in the reference. Hence, one trained in the art would be motivated to make compounds with alternate choices [sic] substituents with guidance provided in the reference and expect these compounds have the same use taught for exemplified compounds in the reference." Respectfully, if that were sufficient, *Takeda* would have come out the other way: the prior art genus taught that its compounds had antidiabetic activity, and it taught a genus that included Actos. Nevertheless, that plainly does not render all such compounds 'obvious', even ones that closely resemble a species that was disclosed in the prior art. Both in *Takeda* and in the present situation, even if there is overlap of the challenged claims with a genus in the prior art, such overlap does not establish *prima facie* obviousness: the prior art must provide reasons for a person of ordinary skill to select a particular starting point and to make the "specific molecular modifications" relied upon in the obviousness analysis. The mere fact that the prior art genus 'permits' such modifications is not sufficient. This rejection is contrary to the obviousness standard for a chemical invention as clarified by *Takeda* and the numerous decisions cited by the majority in *Takeda*. The instant rejection does not meet the standards in *Takeda*, and it should be withdrawn.

Furthermore, the dependent claims include additional structural limitations that are not even discussed in the rejection. No basis to allege that Cai discloses the limitations of any of claims 4-19 was provided. Again, as *Takeda* emphasizes, a *prima facie* case of obviousness is not established by mere overlap with a prior art genus. The Examiner bears the burden of demonstrating that the prior art renders obvious the additional limitations of the dependent claims, and that again requires showing that the reference provides motivation to make the "specific molecular modifications" represented by the dependent claims. No *prima facie* case for an

obviousness rejection has been presented for those claims, and the rejections of those claims should be withdrawn.

Claim 23 was included in this rejection, and is now presented as an independent claim, claim 25. The rejection of claim 23 was clearly improper, though, since the Examiner did not provide any evidence that Cai discloses or suggests treatment of liver fibrosis. Accordingly, new claims 25 and 26, drawn to treatment of liver fibrosis, are patentable over Cai for this additional reason.

Claims 1, 4-19 and 22 were rejected as allegedly obvious in view of Kleeman, et al. Again, this rejection is described as being "maintained" and differs little from what the Examiner has previously presented. The Applicants again traverse this rejection for all the reasons previously presented as further explained herein, and as further supported by *Takeda*.

The Examiner begins with the premise that "Kleeman et al. teaches several pyrimidine compounds, which include compounds claimed in the instant claims…See Table X for various compounds, which include instant compounds." That is, of course, incorrect : Kleeman does not teach any compounds within the scope of the present claims. Rather, this rejection actually relies on generic disclosures of Kleeman and alleged 'equivalence' of certain features.

The Examiner properly recognized that an obviousness analysis should be based on the *Graham v John Deere* factors, but clearly erred in describing the content of the prior art. According to the examiner, while Kleeman does not teach compounds where X of the present claims is S or NH, "Kleeman et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited for formula I….Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make variously substituted pyrimidine compounds as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above."

Contrary to the Examiner's statements, the prior art does NOT teach "equivalency" of the substituents or features of the compounds in its broad generic. It recites certain alternatives for its group X, implying that those are believed to be operative. However, that does NOT amount to evidence of "equivalency". As an illustration, Kleeman also teaches "m represents an integer from 0 to 5" (see claim 1 of Kleeman): nevertheless, that does NOT establish that "0" is equivalent to "5"! A rejection based on equivalency, as the applicants have pointed out before, requires the Examiner to show that the 'equivalency' was recognized in the prior art; merely showing that two alternatives are both considered operable in the prior art genus is plainly insufficient. See, e.g., MPEP 22144.06.

The Examiner is invited to provide some evidence that O and S were known in the art to be "equivalent" in the context of Kleeman; no such evidence has been provided to date. That either might work in the Kleeman genus is not evidence of equivalence. On the other hand, there is direct **evidence** in Kleeman that O and S were NOT considered equivalent. Kleeman teaches a preferred subgenus where X is expressly limited to O (see claims 7 and 8 in Kleeman). At column 3, lines 35-36, Kleeman says, "particularly good results in control of weeds are achieved with compounds wherein X represents an oxygen atom." and the numerous species exemplified in Kleeman *all* contain Oxygen for X. No examples with X = S were described. This is unrebutted evidence that Kleeman does NOT consider O and S to be 'equivalent', and in view of this, Kleeman cannot support an obviousness rejection under the standard applied in *Takeda*.

The Examiner said, "First of all, Kleeman permits X=O and X=S as much as applicants are permitting X=NR and X=S in currently pending claims. It should be pointed out the original claims had X=O as well. Therefore alternate choices should be given equal weight whether it is instant application or a reference."

First, what the present application says is ABSOLUTELY IRRELEVANT to the obviousness analysis. It is not part of the prior art, and could not have been known to the person of ordinary skill prior to the present invention. That is the Only perspective from which an obviousness assessment can properly be made. References to the applicant's disclosure indicate

that the rejection is Relying upon hindsight, biased by the applicants' disclosure, rather than on the proper obviousness perspective.

Second, Kleeman 'permits' "X" to be O or S; and it teaches an express preference for X=O. As a matter of law, mere recitation of alternatives that are alleged to be usable in the prior art genus is NOT a teaching of "equivalence." In the obviousness analysis as described in Takeda, even if the difference looks small *in hindsight*, there must be a reason shown to make the "specific molecular modifications" that the obviousness analysis relies upon—otherwise, the analysis can always be based on hindsight. Even if a particular starting point from Kleeman were selected, the Examiner must explain what would have led one of ordinary skill in the art to replace "O" in a compound from Kleeman with "S". It cannot be based on "equivalence," as there is direct, unrebutted evidence that Kleeman itself recognized NON-equivalence of O and S. Thus no *prima facie* case for obviousness has been established, and this rejection should be withdrawn.

Moreover, the rejection based on Kleeman also fails to show that the other required features of the claimed compounds would have been obvious from the reference. For example, nothing in Kleeman was shown to suggest compounds of the present invention wherein X = NR. The Examiner rejected claim 17, where X = NH, also based on Kleeman, but nothing in Kleeman remotely suggests X = NH. The rejection based on Kleeman appears to rely on the Examiner's comments about the applicant's disclosure, permitting X to be O, S or NR. However, (a) that is NOT a teaching of equivalence, and (b) it is NOT part of the prior art. Thus no prima facie case for rejection of claim 17 exists, and this rejection must be withdrawn.

In the wake of *KSR v. Teleflex*, the PTO has issued its own interim guidelines for examination. It concludes that "in formulating a rejection under 35 USC 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." That has not been done in a way that meets the standards in *Takeda*: even if the prior art genus 'permits' combinations within the present claim scope, that is not enough to render the claims obvious. If that were sufficient, a prior art genus would render obvious all it encompasses, and the prior art genus in

Takeda would have rendered Actos *prima facie* obvious, which it did not. Mere similarity of the claimed invention to a prior art species is also insufficient, unless the prior art provides motivation to make the 'specific molecular modifications' required to arrive at the claimed invention. Thus *Takeda* demonstrates clearly that, even in the wake of *KSR*, neither Cai nor Kleeman has been shown to establish a *prima facie* case for an obviousness rejection. In view of *Takeda*, these rejections should be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 219002029400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 21, 2007

Respectfully submitted,

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